(Ohtoshi et al., 1997, Mol Gen Genet 254, 562-570). In addition to mechanisms to control the onset of DNA replication, other mechanisms contribute to restrict DNA replication to occur only once during the cell cycle. For example, the CDC16, CDC23 and CDC27 proteins are part of a high molecular weight complex, known as the anaphase promoting complex (APC) or cyclosome, (see Romanowski and Madine, Trends in Cell Biology 6, 184-188, 1996, and Wuarin and Nurse, Cell 85, 785-787 (1996), both incorporated herein by reference). The complex in yeast is composed of at least 8 proteins, the TPR (tetratricopeptide repeat) containing proteins CDC16, CDC23 and CDC27, and five other subunits named APC1, APC2, APC4, APC5 and APC7 (Peters et al. 1996, Science 274, 1199-1201). The APC targets its substrates for proteolytic degradation by catalyzing the ligation of ubiquitin molecules to these substrates. APC-dependent proteolysis is required for the separation of the sister chromatids at meta- to anaphase transition and for the final exit from mitosis. Among the APC-substrates are the anaphase inhibitor protein Pds1p and mitotic cyclins such as cyclin B, respectively (Ciosk et al. 1998, Cell 93, 1067-1076; Cohen-Fix et al. 1996, Genes Dev 10, 3081-3093; Sudakin et al. 1995, Mol Biol Cell 6, 185-198; Jorgensen et al. 1998, Mol Cell Biol 18, 468-476; Townsley and Ruderman 1998, Trends Cell Biol 8, 238-244). To become active as a ubiquitin-ligase, at least CDC16, CDC23 and CDC27 need to be phosphorylated in the M-phase (Ollendorf and Donoghue 1997, J Biol Chem 272, 32011-32018). Activated APC persists throughout G1 of the subsequent cell cycle to prevent premature appearance of B-type cyclins which would result in an uncontrolled entry into S-phase (Irniger and Nasmyth 1997, J Cell Sci 110, 1523-1531). It has been demonstrated in yeast that mutations in either of at least two of the APC components, CDC16 and CDC27, can result in DNA overreplication without intervening passages through M-phases (Heichman and Roberts 1996, Cell 85, 39-48). CDC16,CDC23

and CDC27 all are tetratricopeptide repeat (TPR) containing proteins. A suggested minimal consensus sequence of the TPR motif (SEQ ID No 16) is as follows: X_3-W-X_2-L-G-X_2-Y-X_8-A-X_3-F-X_2-A-X_4-P-X_2 (Lamb et al. 1994, EMBO J 13, 4321-4328; X denotes any amino acid, X_n a stretch of n of such amino acids). However, the consensus residues can exhibit significant degeneracy and little or no homology is present in non-consensus residues. The hydrophobicity and size of the consensus residues, rather than their identity, seems to be important. TPR motifs are present in a wide variety of proteins functional in yeast and higher eukaryotes in mitosis (including the APC protein components CDC16, CDC23 and CDC27), transcription, splicing, protein import and neurogenesis (Goebl and Yanagida 1991, Trends Biochem Sci 16, 173-177). The TPR forms a α helical structure, tandem repeats organize into a superhelical structure ideally suited as interfaces for protein recognition (Groves and Barford 1999, Curr Opin Struct Biol 9, 383-389). Within the α helix, two amphipathic domains are usually present, one at the NH_2-terminus and the other near the COOH-terminus (Sikorski et al. 1990, Cell 60 ,307-317).

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Please replace paragraph [0014] on page 5 as follows:

The novel exon encoded by amino acid sequence SEQ ID No 3 (DVIEKKDGPCSGTKGFRAPE) is part of Domain VIII of protein kinases. Mutagenesis has implicated a role of this domain in the catalytic activity (Hawks et al., 1988). In the sequence TKGFRAPE (SEQ ID No 17), the amino acids Threonine (T), Phenylalanine and Alanine (A) are highly conserved, and the Glutamic Acid (E) is invariant. Moreover, substitution of the corresponding threonine in the yeast CDC7 homologue (position 281 of the yeast CDC7; position 722 in SEQ ID No 1) to a glutamate resulted in a dominant-negative CDC7 mutant (Ohtoshi et al. 1997, Mol Gen Genet 254, 562-570).

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Please replace paragraph [0116] on pages 32-33 as follows:

In figures 3 and 4, the complete cDNA sequence of CDC7 (SEQ ID No 8) and CDC27A1 (SEQ ID No 9), respectively, according to the present invention are depicted, with the respective encoded amino acid sequence therebelow (SEQ ID No 1 and SEQ ID No 5). The middle sequence represents the complementary DNA strand of CDC7 (SEQ ID No 26) and CDC27A1 (SEQ ID No 27). Vertical lines in the nucleotide sequence indicate the exon boundaries, i.e. $^{2}|^{3}$ is the boundary between exons 2 and 3. The exon boundaries are derived from genomic CDC7 and CDC27A1 sequences (see examples 1 and 2 respectively). Such lines are also drawn in the amino acid sequence, although, as is indicated above, the amino acids, flanking such a vertical line, may be partially encoded by the adjacent exon. Exact positioning of the vertical line is in such a case not possible and is set at the left or the right of such an amino acid in an arbitrary manner. See examples 1 and 2 for further details.

Please replace paragraph [0121] on page 34 as follows:

Conserved regions of the *Saccharomyces cerevisae* and *Schizosaccharomyces pombe* CDC7 homologue genes were used to synthesize degenerated oligonucleotides to amplify an *Arabidopsis* CDC7 homologue cDNA fragment. These oligonucleotides were as follows:

1 (sense):

5'AAA/G ATA/C/T GGA/C/G/T GAA/G GGA/C/G/T ACA/C/G/T TT 3' (SEQ ID No 18)

2 (sense):

5' ATA/C/T ATA/C/T CAC/T AGA/G GAA/G ATA/C/T AA 3' (SEQ ID No 19)

3 (antisense)

5' AG C/TTC A/C/G/TGG A/C/G/TGC C/TCT A/GAA A/C/G/TCC 3' (SEQ ID No 20)

4 (antisense)

A4

5' AC A/C/G/TCC A/C/G/TA/GC A/GCT CCA A/C/G/TAT A/GTC 3' (SEQ ID No 21)

Please replace paragraph [0125] on page 35 as follows:

Upon comparison with the genomic *Arabidopsis sequence*, it however appeared that the present cDNA was not complete. To complete our cDNA at the 5' side we used the CAP-finder kit (Clontech), using the primers (CTCTCCCATCTGGTCATGTC, #1 SEQ ID No 28); GAACATGCAGTAGCCGTACC, #2 (SEQ ID No 29)) specified for the cDNA, in nested PCR reactions. For the missing 3' end, two nested sequences specific for the cDNA (AAATGGTGCGAACTCAACAC, #2 (SEQ ID No 30)) and

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(TATGGGAAGTAGCCAAGCTG, #1 (SEQ ID No 31)) and an anchored oligo-dT on the lower strand were used. PCR conditions were essentially as described (Ferreira et al., 1991). The fragments were eluted from agarose gel and cloned using standard techniques and sequenced. The deduced amino acid sequence encoded by the PCR fragment showed clear homology to the yeast published CDC7 sequences and matched with an the above mentioned *Arabidopsis* genomic sequence. The DNA-fragment, comprising the missing 5' terminal sequence, comprised an additional coding sequence of 63nt (nrs 122340 to 122278 in Z97342) not identified in Z97342, coding for the amino acid sequence of SEQ ID NO 2.

Please replace paragraph [0128] on page 36 as follows:

Conserved regions of the published CDC27 homologue genes (Sikorski et al., 1991 Cold Spring Harbor Symposia on Quantitative Biology vol LVI, 663-673, 1991) were used to synthesize degenerated oligonucleotides to amplify *Arabidopsis* CDC27 cDNA. The oligonucleotides were as follows:

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1 (sense):

5' TGG GTA/C/G/T TTA/G GCA/C/G/T A/CAA/G GG 3' (SEQ ID No 32)

2 (sense):

5' ATG GAA/C/G/T G/ATT/C/A TA/TC/T AGA/C/G/T AC 3' (SEQ ID No 33)

3 (antisense)

5' AGA/G CAT/C TAT/C AAT/C GCA/C/G/T TGG 3' (SEQ ID No 34)

4 (antisense)

5' TA T/A/G AC/T CAT A/C/G/TCC C/TAA A/C/G/CC A/GAA 3' (SEQ ID No 35)

Please replace paragraph [0144] on pages 40-41 as follows:

First-strand cDNA was prepared from RNA isolated from different *Arabidopsis thaliana* tissues (etiolated seedlings, flowers, flower buds; stems; leaves; roots; siliques) and from *Arabidopsis thaliana* root cultures treated for 48 h with different chemical substances (10^{-6} M abscisic acid; 10^{-7} M 2,4-dichlorophenoxyacetic acid; 100 mM hydroxyurea; 10^{-6} M kinetin; 10^{-6} M kinetin + 10^{-6} M 1-naphthaleneacetice acid; 10^{-6} M 1-naphthaleneacetic acid; 2% (w/v) oryzalin). PCR was performed with these cDNAs using CDC27A-specific primers (sense primer 5' CCG TAG TGC TAG AAT AGC A 3' (SEQ ID No 22) and antisense primer 5' AGT CAG CGT TGA AGT c3' (SEQ ID No 23)) or CDC27B-specific primers (sense primer 5' TCT CTC GAG GAA GAA AGG CAA CAA 3' (SEQ ID No 24) and antisense primer 5' GGT TCT TGG AGT AGC TAT GGT TTC 3' (SEQ ID No 25)). The resulting fragments generated by PCR were seperated in an agarose gel, blotted to a nylon membrane and hybridized with an ^{32}P labeled CDC27A or CDC 27B DNA probe. Results are shown in Figure 7 for CDC27A where the arrows indicate the presence of 2 bands, differing by 30 nucleotides. Sequencing of both fragments showed that they are identical, except for the 30 bp insertion. Figure 8 illustrates the results for CDC27B.

Please replace paragraph [0148] on page 42 as follows: